The interaction between prefrontal cortex and reward system in pathological gambling: evidence from neuroscientific data

D i s s e r t a t i o n

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von Dipl.-Psych. Saskia Quester (geb. Köhler)

Präsident der Humboldt-Universität zu Berlin: Prof. Dr. Jan-Hendrik Olbertz
Dekan der Mathematisch-Naturwissenschaftlichen Fakultät II: Prof. Dr. Elmar Kulke

Gutachter/Gutachterin: 1. Prof. Dr. Elke van der Meer
2. Prof. Dr. Andreas Heinz
3. Prof. Dr. Wim van den Brink

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Summary

Pathological gambling (PG) is a psychiatric disorder newly classified under the same category as substance use disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Theories on addiction emphasize the role of the prefrontal cortex (PFC) and the mesolimbic reward system (especially the ventral striatum) in the development and maintenance of addictive behavior. Accordingly, neuroimaging studies on substance-related addictions reported functional and structural changes in fronto-striatal circuits. For PG, neuroimaging findings are not that extensive as for substance use disorders, but also demonstrate altered reward processing and prefrontal function. However, there is a lack of studies focusing on different aspects of functional and structural correlates within these areas in PG.

This thesis investigated PG patients, alcohol dependent (AD) patients and healthy controls with magnetic resonance imaging (MRI) in order to fill this gap and to expand neurobiological findings in a behavioral addiction such as PG. Brain responses during reward processing in a reward paradigm, brain structural images and intrinsic brain responses during resting-state were acquired and analyzed in three steps: In *analysis I*, data of the task was compared between the three groups. In *analysis II,* local gray matter volume of PG patients and controls was processed via voxel-based morphometry. Resting-state data of PG patients and controls was analyzed via seed-based functional connectivity in *analysis III*.

The following main results were observed: First, PG patients showed increased brain responses in right ventral striatum during the prospect of possible monetary loss compared to controls and AD patients, and decreased brain responses in right ventral striatum and right medial PFC during the notification of successful avoidance of monetary loss as compared to controls. Second, PG patients showed an increase in local gray matter volume in right ventral striatum and right PFC. Third, the functional connectivity between PFC and striatal areas was increased in PG patients.

Our results add further evidence for an altered reward processing in PG and underline the importance of loss avoidance processing. Moreover, our findings of volumetric alterations within and increased connectivity between PFC and reward system, suggest an altered interaction between these brain regions. Since such alterations in cortico-striatal circuits resemble those reported for substance-related additions, our findings support the new classification of PG along with substance use disorders in the DSM-5.

Zusammenfassung

Pathologisches Spielen (PG) ist eine psychiatrische Erkrankung, die gerade erst in der fünften Ausgabe des „Diagnostischen und Statistischen Manual Psychischer Störungen“ (DSM-5) der gleichen Kategorie wie substanzgebundene Suchterkrankungen zugeordnet wurde. Gängige Suchttheorien schreiben dem präfrontalen Kortex (PFC) und dem mesolimbischen Belohungssystem (d.h. ventrales Striatum) eine bedeutende Rolle in der Entstehung und Aufrechterhaltung von Suchtverhalten zu. Bildgebungsstudien zu Substanzabhängigkeit beobachteten funktionelle und strukturelle Veränderungen in fronto-striatalen Systemen. Bezüglich der PG ist die Studienlage nicht derart vielfältig wie für Substanzabhängigkeit; es wurden allerdings ebenfalls Veränderungen in der Verarbeitung von Belohnungen im ventralen Striatum und präfrontaler Funktion berichtet. Jedoch gibt es kaum Studien zu PG, die sich mit verschiedenen Aspekten funktioneller und struktureller Korrelate in diesen Regionen beschäftigen.

Um diese Lücke zu füllen und die Erforschung der Neurobiologie der PG voranzutreiben, untersuchte die vorliegende Doktorarbeit Patienten mit PG, alkoholabhängige (AD) Patienten und gesunde Kontrollpersonen mittels Magnetresonanztomografie. Es wurde die Gehirnaktivität während der Verarbeitung von Belohnung, die Gehirnstruktur und die intrinsische Gehirnaktivität unter einer Ruhebedingung gemessen und in drei Schritten analysiert: In *Analyse I* wurde die Gehirnaktivität während der Belohnungsaufgabe zwischen den drei Gruppen verglichen. In *Analyse II* wurde das Volumen lokaler grauer Substanz von PG Patienten und Kontrollpersonen mittels voxelbasierter Morphometrie analysiert. In *Analyse III* wurde die intrinsische Gehirnaktivität der PG Patienten und Kontrollpersonen mittels einer seedbasierten funktionellen Konnektivitätsanalyse ausgewertet.

Die folgenden Hauptergebnisse wurde gefunden: (1) PG Patienten zeigten eine erhöhte Aktivierung im rechten ventralen Striatum während der Antizipation von Geldverlust im Vergleich zu AD Patienten und Kontrollen, und eine verminderte Aktivität im rechten ventralen Striatum und rechten medialen PFC während der Rückmeldung über die Verhinderung eines Geldverlusts im Vergleich zu den Kontrollen. (2) PG Patienten wiesen ein erhöhtes Volumen grauer Substanz im rechten ventralen Striatum und rechten PFC auf. (3) Die funktionelle Konnektivität zwischen dem PFC und striatalen Arealen war in den PG Patienten erhöht.

Diese Ergebnisse liefern weitere Hinweise für eine veränderte Belohnungsverarbeitung in PG und betonen die Bedeutung der Verarbeitung von Verlustvermeidung. Des Weiteren

deutet das Ergebnis der Volumenveränderungen im und der erhöhten Konnektivität zwischen dem PFC and Belohnungsystem auf eine veränderte Interaktion zwischen diesen Gehirnregionen hin. Da solche Veränderungen in kortikostriatalen Systemen Ähnlichkeiten zu denen in substanzgebundenen Abhängigkeiten aufweisen, unterstützen unsere Ergebnisse die neue Klassifikation der PG im DSM-5 zusammen mit Substanzabhängigkeiten.

List of papers

This thesis is based on the following original papers:

Analysis I

Romanczuk-Seiferth, N.[*], **Koehler, S.**[*], Dreesen, C., Wüstenberg, T., Heinz, A. (2014). Pathological gambling and alcohol dependence: neural disturbances in reward and loss avoidance processing. *Addiction Biology*. Epub ahead of print, doi: 10.1111/adb.12144

Analysis II

Koehler, S., Hasselmann, E., Wüstenberg, T., Heinz, A., Romanczuk-Seiferth, N. (2013). Higher volume of ventral striatum and right prefrontal cortex in pathological gambling. *Brain Structure and Function*. Epub ahead of print, doi: 10.1007/s00429-013-0668-6

Analysis III

Koehler, S., Ovadia-Caro, S., van der Meer, E., Villringer, A., Heinz, A., Romanczuk-Seiferth, N., Margulies, D.S. (2013). Increased functional connectivity between prefrontal cortex and reward system in pathological gambling. *PLoS ONE* 8(12): e84565.

[*] Authors contributed equally.

List of abbreviations

AD	Alcohol dependent / dependence
BIS-10	Barratt Impulsiveness Scale-Version 10
BOLD	Blood-oxygen-level-dependent
BPM	Biological parametric mapping
CS	Conditioned stimulus /stimuli
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWHM	Full-width at half maximum
G-SAS	Gambling Symptom Assessment Scale
ICD-10	International Classification of Diseases, tenth revision
KFG	"Kurzfragebogen zum Glücksspielverhalten"
MID	Monetary incentive delay
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PG	Pathological gambling
PFC	Prefrontal cortex
ROI	Region of interest
SVC	Small volume correction
VBM	Voxel-based morphometry

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1 Introduction

Pathological gamblers are not able to resist the temptation to gamble even though the consequences are severe (i.e., impoverishment and break-up of personal relationships). Since pathological gambling (PG) is a heavy burden for affected people and society, a better understanding of underlying neurobiological mechanisms is of high interest. By using magnetic resonance imaging (MRI), this thesis aimed to investigate the neurobiological underpinnings of an insufficient capacity to control and stop the maladaptive gambling in PG. The focus of our analyses therefore was on brain regions implicated in inhibitory control and reward processing and how they are functionally coupled.

2 Theoretical background

2.1 General overview of pathological gambling

PG is a psychiatric disorder with a prevalence of around 0.5 % in Germany (Erbas & Buchner, 2012) and more often diagnosed in males than females (Gray, 2004). High proportions of subjects with PG in Germany were found among game machine users (8.7 %), horse race bettors (6.7 %) and casino gamblers (5.2 %) (Buth & Stöver, 2008). Since PG shares clinical characteristics (e.g., loss of control and craving) as well as common cognitive and personality features, neurobiological processes and genetic vulnerability with substance use disorders (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005; Grant, Potenza, Weinstein, & Gorelick, 2010; Leeman & Potenza, 2012; Potenza, 2008; Slutske, Ellingson, Richmond-Rakerd, Zhu, & Martin, 2013), it has been considered as a behavioral addiction (Grant et al., 2010). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013), PG is now classified as “gambling disorder” under the category “Substance-Related and Addictive Disorders”.

Central for the concept of addiction are the seemingly physical symptoms of substance use disorders, namely tolerance and withdrawal (Edwards, 1990). The brain adapts to the physical effects of the drug so that increased amounts of the drug have to be consumed in order to achieve the same effects (tolerance) and withdrawal symptoms arise when drug consumption is stopped (DSM-5, American Psychiatric Association, 2013). Accordingly, the drug of abuse is repeatedly consumed in order to prevent withdrawal symptoms.

However, PG is not related to the consumption of an exogenous drug; the psychotropic effect is caused by the body's own biochemical alterations that are triggered by the excessive behavior (Grusser, Poppelreuter, Heinz, Albrecht, & Sass, 2007). In contrast to the severe physicals symptoms during detoxification in alcohol or drug dependent patients, PG patients show rather moderate withdrawal-like vegetative symptoms such as restlessness and irritability during abstinences (American Psychiatric Association, 2013; Grusser et al., 2007; Mann, Fauth-Buhler, Seiferth, & Heinz, 2013), which complicates the classification of PG as addiction. On the other hand, craving for the behavior and reduced control are hallmarks of both substance-related and nonsubstance-related addictions (Grusser et al., 2007). Therefore, PG is considered as an addictive disorder in this thesis.

2.2 Theories of addiction

In addition to environmental and genetic factors, psychological and neurobiological factors play an important role in the development and maintenance of substance-related addiction (for an overview see Heinz & Batra, 2003). Learning theoretical approaches focus on model learning (e.g., drug-consuming parents) as well as classical and operant conditioning (Everitt, Dickinson, & Robbins, 2001; Siegel, 1999). In classical conditioning, over the course of drug use neutral stimuli (external: bottle of wine, internal: stress) are associated with the effects of the drug. These cues become conditioned stimuli (CS) and can trigger an urge for the drug ("craving") and approach behavior. Addictive behavior can then be associated with the occurrence of a pleasant feeling (i.e., positive reinforcement) or the disappearance of negative feelings (i.e., negative reinforcement, operant conditioning).

On a neurobiological level, several theories emphasize the role of appetitive processing and inhibitory control (for a review see Limbrick-Oldfield, van Holst, & Clark, 2013). The reward deficiency hypothesis (Blum et al., 1995; Comings & Blum, 2000) claims that the vulnerability for addiction results from an altered reward system, leading to an insensitivity to natural rewards (e.g., food, sex) and drug-seeking in order to elicit reward associated feelings. In contrast, the incentive-sensitization theory (Robinson & Berridge, 1993, 2001) proposes that brain alterations result from repeated drug use, in a way that long-lasting and progressive changes in reward areas are produced, making drug-associated stimuli highly attractive over conventional rewarding stimuli so that drug-seeking is able to control behavior. Another class of theories emphasizes a reduced inhibitory control over reward-indicating impulses (Bechara, 2005; Jentsch & Taylor, 1999). Especially the prefrontal

cortex (PFC) has been proposed as a contributor for the hypothesized decreased cognitive control in addictive behavior (Baler & Volkow, 2006; Bechara, 2005; Goldstein & Volkow, 2011; Park et al., 2010; Volkow et al., 2010). Reduced self-regulatory competencies in addiction have thus been explained by a disturbed balance between PFC and regions involved in reward (Bechara, 2005; Heatherton, 2011; Heatherton & Wagner, 2011). The impaired response inhibition and salience attribution model (Goldstein & Volkow, 2002) combines the concepts of increased salience to drug-related stimuli, undervaluing of conventional reinforcers and deficits in inhibitory control.

On a neurochemical level, alterations in dopaminergic neurotransmission have been implicated in the pathogenesis of addiction (Di Chiara, 1995; Heinz, 2002). The dopaminergic system projects from the ventral tegmental area and substantia nigra to the striatum, and other subcortical and cortical regions, and interacts with other neurotransmitter in a complex manner (Heinz, 2000). Most drugs of abuse cause a release of dopamine in the nucleus accumbens (part of the ventral striatum), which has been associated with the reinforcing effects of drug intake (Wise, 1996). In the frame of the incentive-sensitization theory, chronic drug intake may cause a sensitized dopamine release in response to drug-associated stimuli (CS) and in that way enhances their motivational effects and trigger drug "wanting" (instead of the feeling of pleasure or "liking") (Robinson & Berridge, 1993). On the other hand, long-term alcohol intake was associated with a compensatory down-regulation of dopamine receptor availability in the ventral striatum (Heinz et al., 2004). Moreover, it has been suggested that continuous drug consumption is related to a transition from ventral to dorsal striatal involvement, including its dopaminergic innervation, representing a shift from voluntary to more habitual (often also called "compulsive") drug consumption (Everitt & Robbins, 2005; Ito, Dalley, Robbins, & Everitt, 2002). For behavioral addictions without the effect of an exogenous drug, neuroadaptive alterations may be less pronounced. As a predisposing factor, dysfunctional dopaminergic transmission, originally derived from genetic studies that linked particular alleles of the dopamine receptor genes with substance use disorders (Blum et al., 1990; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991), may result in drug-seeking behavior to stimulate the reward system (reward deficiency hypothesis; Blum et al., 1995; Comings & Blum, 2000).

Together, the above-mentioned neurobiological theories emphasize the role of the PFC and reward areas, especially the ventral striatum, for the development and maintenance of addiction. Indeed, several functional MRI (fMRI) studies have implicated an involvement

of the PFC and the ventral striatum in PG (Balodis et al., 2012; Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005; de Ruiter et al., 2009; Potenza, Leung, et al., 2003; Reuter et al., 2005; van Holst, van Holstein, van den Brink, Veltman, & Goudriaan, 2012; van Holst, Veltman, Buchel, van den Brink, & Goudriaan, 2012; for reviews on neuroimaging studies see Potenza, 2013; van Holst, van den Brink, Veltman, & Goudriaan, 2010a, 2010b). However, to date, we know little about reward processing in PG. Also other neurobiological correlates such as brain volume and intrinsic functional connectivity are rarely investigated in this disorder.

2.3 Reward processing in addiction

Studies using positron emission tomography (PET) in substance use disorders observed alterations in reward-related neurotransmission and metabolism within the mesolimbic reward system (i.e., striatum) (Heinz, 2002; Volkow et al., 1996). For alcohol dependence (AD), fMRI studies reported increased brain responses in response to alcohol-related cues in the ventral striatum (Braus et al., 2001; Heinz, Beck, Grusser, Grace, & Wrase, 2009; Myrick et al., 2004; Wrase et al., 2007), which is activated by conventional reinforcers in healthy controls (Aharon et al., 2001; Knutson, Adams, Fong, & Hommer, 2001; Stark et al., 2005). By testing monetary reward as a secondary reinforcer in substance-related addictions, most fMRI studies used some version of the monetary incentive delay (MID) task (Knutson et al., 2001) (see chapter 4.2.3). The task allows the measurement of brain responses while the participant is asked to respond rapidly to a target in order to gain a reward or avoid a punishment. Several studies on different substance use disorders reported altered brain responses in the ventral striatum during the prospect of monetary gain with more studies observing reduced ventral striatal brain responses in alcohol dependent (AD) patients and smokers (Beck et al., 2009; Peters et al., 2011; Wrase et al., 2007), while elevated ventral striatal brain responses were found in cannabis users and cocaine dependent patients (Jia et al., 2011; Nestor, Hester, & Garavan, 2010), as well as enhanced brain responses in medial PFC during the notification of monetary reward outcome in AD patients, cannabis users and cocaine dependent patients (Bjork, Smith, & Hommer, 2008; Jia et al., 2011; van Hell et al., 2010). Together, these studies suggest alterations in ventral striatal and medial prefrontal reward processing in substance-related addictions.

For PG, PET studies have observed an involvement of neurochemical mechanisms in mesolimbic reward areas in PG (Boileau, Payer, Chugani, Lobo, Behzadi, et al., 2013;

Boileau, Payer, Chugani, Lobo, Houle, et al., 2013; Joutsa et al., 2012; Linnet, Peterson, Doudet, Gjedde, & Moller, 2010) and Parkison's disease with PG behavior (Steeves et al., 2009), however, the findings are less consistent. FMRI studies on PG demonstrated diminished or enhanced brain responses in various brain regions including prefrontal and striatal regions in response to addiction-related stimuli (i.e., gambling scences) (Crockford et al., 2005; Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Potenza, Steinberg, et al., 2003; van Holst, van Holstein, et al., 2012) or monetary reward (de Ruiter et al., 2009; Reuter et al., 2005; van Holst, Veltman, et al., 2012). So far, only two MID studies on PG exist, and observed diminished brain responses in areas of the ventral striatum during the prospect of monetary reward (Balodis et al., 2012; Choi et al., 2012) and in ventromedial PFC during the notification of monetary reward (Balodis et al., 2012). Together, these findings suggest that PG is related to alterations in reward processing. However, a direct comparison between PG and a substance-related addiction using the MID is lacking. Moreover, the above-mentioned studies have focused on the processing of monetary gains and/or the processing of losses, although the MID also provides the condition of successful avoidance of monetary loss. This aspect of loss processing may be especially relevant for the understanding of reward processing in PG, since it serves as a negative reinforcement that in turn may result in behavior with increased extinction resistance compared to positive reinforcement (Solomon, Kamin, & Wynne, 1953).

2.4 Brain structural changes in addiction

Brain alterations and adaptations as proposed by addiction theories may be reflected by changes in brain volume. Studies on AD reported widespread atrophy in gray and white matter, with the most pronounced volume loss in the frontal cortex, but also in a variety of subcortical areas including ventral striatum (Buhler & Mann, 2011; Cardenas, Studholme, Gazdzinski, Durazzo, & Meyerhoff, 2007; Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005; Wrase et al., 2008). Structural alterations in frontal and striatal regions were also observed for other substance use disorders (Chang, Alicata, Ernst, & Volkow, 2007; Li et al., 2013; Moreno-Lopez et al., 2012; Schwartz et al., 2010). For PG, two voxel-based morphometry (VBM) studies (Joutsa, Saunavaara, Parkkola, Niemela, & Kaasinen, 2011; van Holst, de Ruiter, van den Brink, Veltman, & Goudriaan, 2012) did not find any gray matter alterations, whereas another recent study demonstrated decreased hippocampus and amygdala volume in PG patients (Rahman, Xu, & Potenza, 2013). In addition, diffusion tensor imaging studies observed widespread white matter

microstructure abnormalities in PG patients suggesting an alteration in structural brain connectivity (Joutsa et al., 2011; Yip et al., 2013). With respect to a related excessive behavior, a volume increase in left ventral striatum was found in adolescent frequent video game players (Kuhn et al., 2011). However, studies on PG focusing explicitly on gray matter changes in prefrontal and striatal areas are lacking.

2.5 Functional connectivity alterations in addiction

The findings of alterations in both the PFC and areas of the reward system in addiction suggest that also the functional interaction between both systems may be altered. Evidence for an altered interaction between PFC and mesolimbic reward system in addiction comes from functional connectivity studies on substance use disorder. During resting-state fMRI, altered functional connectivity between striatal areas and PFC (Ma et al., 2010; Upadhyay et al., 2010; Wang et al., 2013; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011) was observed in different substance use disorders. Accordingly, impaired fronto-striatal connectivity during decision-making was reported for AD (Park et al., 2010). For PG, an altered functional coupling between prefrontal and mesolimbic structures is most likely, since next to alterations in reward processing, also PFC functioning (inhibitory control, decision-making) seems to be impaired (Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002; de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, 2012; Goudriaan et al., 2005; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006a, 2006b; Potenza, Leung, et al., 2003). However, studies investigating functional connectivity between brain areas in PG are rare. Just recently, two studies observed changes in functional connectivity of different striatal areas during inhibition and decision-making in PG (Peters, Miedl, & Buchel, 2013; van Holst, van der Meer, et al., 2012). A first indication for an altered fronto-striatal functional connectivity in PG was provided by Tschernegg et al. (2013). By using a graph-theoretical approach, they found an increased functional connectivity between caudate and anterior cingulum in PG. However, it remains open whether PG patients demonstrate similar alterations in the interaction between PFC and the core structure of the reward system (i.e., ventral striatum) as reflected by functional connectivity findings in substance-related addictions.

3 Research questions and hypotheses

This thesis aims to investigate underlying neurobiological mechanisms of PG behavior. By focusing on brain regions implicated in inhibitory control and reward processing (i.e., PFC and ventral striatum), the thesis is concerned with reward processing, brain volume and functional connectivity. The following major research questions result from the theoretical background (see chapter 2):

1) Do PG patients show alterations in brain responses during reward processing, especially during the processing of monetary loss and its avoidance?
Analysis I

We hypothesized that PG patients show altered brain responses in areas that have previously been implicated in reward processing during the MID task: the ventral striatum and medial PFC. According to previous studies on PG (Balodis et al., 2012; Choi et al., 2012), we hypothesized diminished brain responses in ventral striatum during the prospect of monetary gain and loss when compared to controls and an altered brain response in this brain region when compared to AD patients due to the different relevance of money for both patient groups. By combining findings on PG and AD (Balodis et al., 2012; Beck et al., 2009; Bjork et al., 2008; Reuter et al., 2005), we assumed that PG patients show a reduced ventral striatal and medial prefrontal brain response during obtaining monetary gain compared to controls and AD patients. Studies investigating successful loss avoidance in PG are lacking. However, we assumed that PG patients would differ in ventral striatal and medial prefrontal brain responses from controls as well as AD patients due to the relevance of this aspect of reward processing in PG.

2) Do PG patients have gray matter alterations within structures of the PFC and the mesolimbic reward system?
Analysis II

We hypothesized that PG patients show changes in local gray matter in the PFC and ventral striatum.

3) Do PG patients demonstrate alterations in functional connectivity between prefrontal and mesolimbic structures?
Analysis III

Due to our findings of an increased volume in local gray matter in right PFC and right ventral striatum in PG patients *(analysis II)*, we hypothesized to find an altered resting-state functional connectivity between these structures.

4 Methodological background

4.1 Participants

Seventy subjects participated in an MRI study at the Charité, Campus Benjamin Franklin − Universitätsmedizin Berlin, Germany from 06/2010 till 06/2011. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Charité − Universitätsmedizin Berlin. Details of the final sample sizes are given in Figure 1. We recruited PG patients via Internet advertisement and notices in casinos. Diagnosis for PG was assessed with a German screening instrument (see 4.2.2), which is based upon the diagnosis criteria of the DSM-IV and the tenth revision of the International Classification of Diseases (ICD-10). PG patients were neither abstinent from gambling nor in therapy. AD patients were recruited from an inpatient detoxification ward, where a psychiatrist confirmed diagnosis AD according to DSM-IV/ICD-10 criteria and exclusion of PG diagnosis. None of the participants had a known history of any neurological disorder or current psychiatric Axis I disorder including alcohol (for PG patients and controls) or drug dependence as verified by an interview according to the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I, First, Spitzer, Gibbon, & Williams, 2001). In all analyses, groups were matched for possible influencing factors (e.g., age, smoking, fluid intelligence, alcohol intake), or these variables were used as covariates.

4.2 Data acquisition

4.2.1 Setting and procedure

Participants gave written informed consent and underwent a questionnaire and instruction session. Afterwards, they attended a 75 minutes MRI session, which was performed on a 3 Tesla Siemens Magnetom Tim Trio (Siemens, Erlangen, Germany). The first MRI measurement was a T1-weighted three-dimensional magnetization prepared rapid gradient echo sequence (*analysis II*, for anatomical registration in *analyses I* and *III*). Subsequent, three experimental tasks were performed in the following fixed order: (1) the MID task *(analysis I)*, (2) a stock market game to measure resisting a temptation (Walter et al.), and

(3) a loss aversion paradigm adapted from Tom, Fox, Trepel, and Poldrack (2007). Tasks (2) and (3) are not part of this thesis. As final measurement, we acquired a 5 minutes eyes-closed resting-state fMRI (*analysis III*).

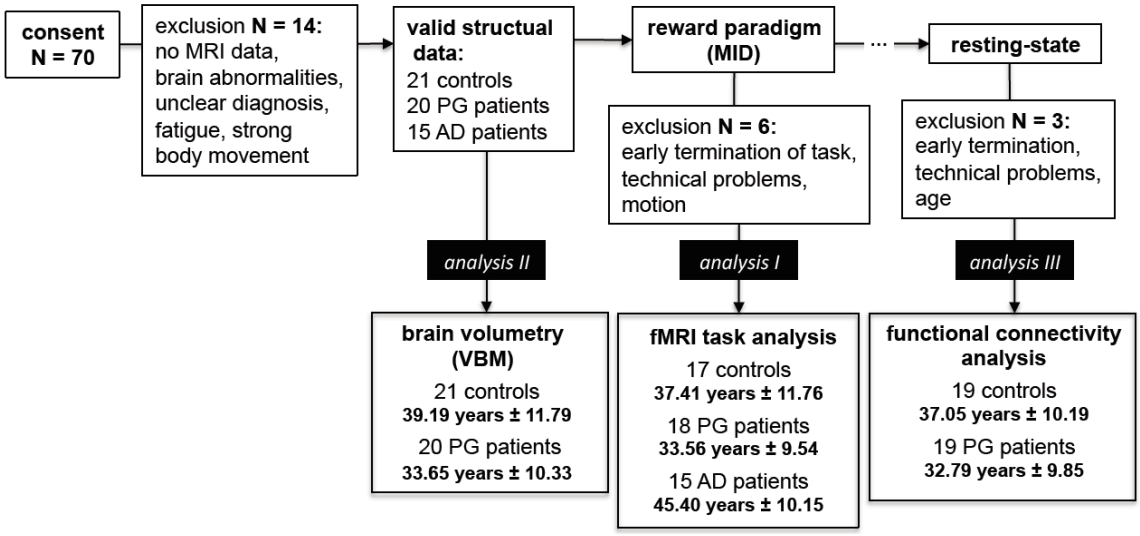

Figure 1. Sample sizes: number of subjects changed during the process from given consent, over participation, to the different analyses.

4.2.2 Screening instruments and questionnaires

The following instruments were used:

- PG diagnosis and symptom severity: German short questionnaire for gambling behavior "*Kurzfragebogen zum Glücksspielverhalten*" (KFG, Petry & Baulig, 1996); cut-off score for a diagnosis is 16; gamblers with a higher score were included
- PG symptom severity: German version of the *Gambling Symptom Assessment Scale* (G-SAS, Kim, Grant, Potenza, Blanco, & Hollander, 2009)
- fluid intelligence: *Wechsler Intelligence test for adults,* matrices test (Aster, Neubauer, & Horn, 2006)
- impulsiveness: German version of the *Barratt Impulsiveness Scale-Version 10* (BIS-10), three impulsiveness sub-scores: nonplanning, motor and cognitive impulsiveness (Preuss et al., 2008)
- desire to gamble (craving): visual analog scale with five craving-related questions, agreement marked by a line between 0 (‘‘not at all’’) and 100 % (‘‘extremely strong’’)

4.2.3 Experimental task

In order to investigate brain responses (i.e., the blood-oxygen-level-dependent [BOLD] signal) during reward processing *(analysis I)*, we applied a modified version of the MID task developed by Knutson et al. (2001). During each trial of the task, subjects saw geometric symbols (cues), which indicated that they may either win or lose money (1 €) or are in a neutral trial; subjects then waited for a variable anticipatory delay period. Finally, subjects were asked to respond as fast as possible with a button press to a rapidly presented target. A feedback informed subjects of whether they won or lost money. The task lasted 12 minutes and consisted of 25 gain, 25 loss, and 25 neutral trials, presented in a random order. An adaptive algorithm guaranteed a success on about 67 % of the trials. Before the actual experiment, subjects practiced the task outside the MRI in order to learn the association between cue and outcome. Figure 2 depicts an example trial.

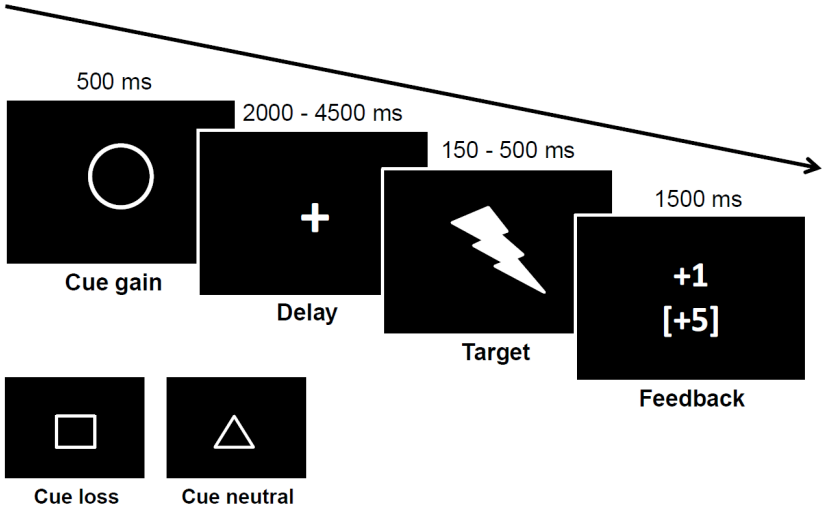

Figure 2. Experimental paradigm: Upper row shows an exemplary gain trial (cue is a circle) in the MID with feedback about gain outcome (+1 €) and current account balance ([+5 €]). Lower row shows cues for loss (rectangle) and neutral (triangle) trials.

4.2.4 Resting-state fMRI

In the absent of a task while the participants were "just" resting in the scanner, we measured the spontaneous fluctuations of the BOLD signal. This method is known as resting-state fMRI. It has the advantage of no direct effects of task demands and a relatively short duration of scan is sufficient for reliable correlation-based results (Van Dijk et al., 2010). We used the data from the resting-state measurement for *analysis III*.

4.3 Data analysis

4.3.1 Data preprocessing

Functional data was preprocessed using the following steps: slice-time correction, motion correction, spatial smoothing (with a full-width at half maximum (FWHM) Gaussian kernel of 8 mm for *analysis I* and 6 mm for *analysis III*), coregistration, and normalization to the standard Montreal Neurological Institute (MNI) brain template. Subjects who moved more than 4 mm and rotate more than 4 degree were excluded (for analysis *I* one PG patient; for *analysis III* no movement artifacts). Structural data were segmented into gray matter, white matter and cerebrospinal fluid and normalized to the stereotactical standard space (Ashburner, 2007). Gray matter maps were spatially smoothed with a Gaussian kernel of 8 mm FWHM.

4.3.2 Regions of interest

Since our hypotheses about anatomical regions of interest within the PFC and reward system were mainly based on functional findings, we used regions of interests (ROIs) from a probabilistic publication-based MNI atlas (http://neuro.imm.dtu.dk/ services/jerne/ninf/voi.html; access 2011) in *analyses I* and *II*. These ROIs were based on data recorded in the original BrainMap database of published functional and structural neuroimaging experiments (Fox & Lancaster, 1994). For *analysis I*, we used ROIs, which were reliably related to reward processing during the MID task (Bjork et al., 2004; Knutson et al., 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003), namely the bilateral ventral striatum (depicted in red in Figure 3) and medial PFC (depicted in blue in Figure 3). The bilateral ventral striatum was also used as ROI for *analysis II.* Moreover, in *analysis II* we concentrated on the right PFC (depicted in blue in Figure 3) rather than the medial PFC, since it plays a role in inhibitory control and self-regulation (Aron, Robbins, & Poldrack, 2004; Buchsbaum, Greer, Chang, & Berman, 2005; Cohen & Lieberman, 2010; Knoch & Fehr, 2007; Simmonds, Pekar, & Mostofsky, 2008). ROIs for functional connectivity analysis *(analysis III)* were based on the VBM results *(analysis II)*. Spheres were defined at the peak points of the gray matter differences in right middle frontal gyrus and right ventral striatum (depicted in green in Figure 3). We chose the radii spheres such that the significant cluster from the VBM analysis would correspond to the size of the sphere.

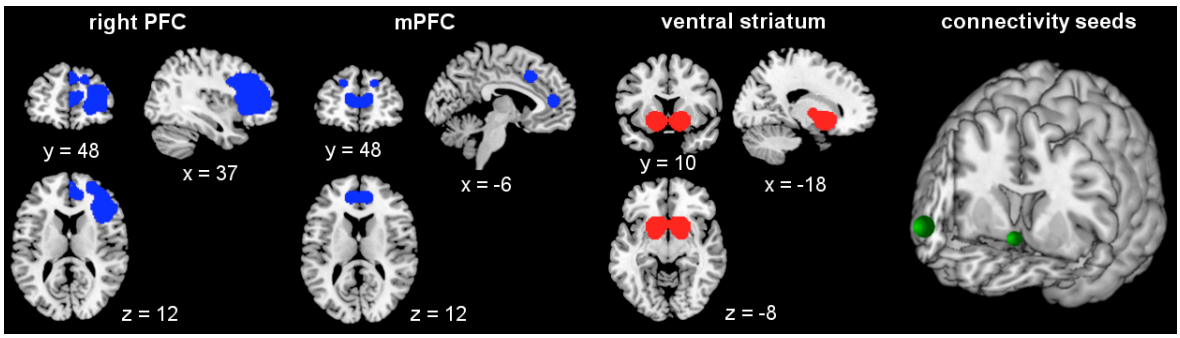

Figure 3. Regions of interest (ROIs). PFC (in blue) and the ventral striatum (in red) for *analyses I & II*. Right middle frontal seed (x = 44, y = 48, z = 7) and right ventral striatal seed (x = 5, y = 6, z = -12) depicted in green for *analysis III*. Coordinates are given in MNI space.

4.3.3 Brain volumetry

The most popular morphometric method is VBM (for a detailed description see Ashburner & Friston, 2000). It uses a standard brain template in order to spatially normalize the participants' brains to the same stereotactic space and makes changes in the local concentration of gray matter on a voxel-wise level visible. We applied VBM in *analysis II* and used the individual gray matter images to analyze group differences in brain structure. We performed a voxel-wise whole-brain group comparison using a threshold of $p < .001$ (uncorrected) for exploratory purpose. For the testing of our ROIs, we conducted a small volume correction (SVC) with a significant threshold of $p < .05$, family-wise error (FWE) corrected for multiple comparisons. We further used VBM in *analysis I* to receive individual gray matter images, which were then used as voxel-wise covariate in the group statistics (see chapter 4.3.4).

4.3.4 fMRI task

For the analysis of the MID task *(analysis I)*, we computed the following contrast images: *gain cue > neutral cue* and *loss cue > neutral cue* for the anticipation phases, *successful gain outcome > nonsuccessful gain outcome* and *successful loss avoidance outcome > nonsuccessful loss avoidance outcome* for the feedback phases. Since AD is related to widespread brain tissue loss (Beck et al., 2012; Cardenas et al., 2007; Demirakca et al., 2011), which most likely affects brain responses and thus group differences, we used the individual gray matter volume as voxel-wise covariate in the group statistics as implemented in the biological parametric mapping (BPM) toolbox (Casanova et al., 2007). Statistical values were thresholded with a SVC-adjusted significant threshold of $p < .05$, family-wise error (FWE) corrected for multiple comparisons.

4.3.5 Resting-state functional connectivity

In *analysis III*, we computed whole brain correlation maps for the right middle frontal seed and the right ventral striatal seed. This computational method is called resting-state functional connectivity. Whole brain connectivity maps were then compared between and within groups. Group level results for connectivity maps were thresholded at a $z > 2.3$, corrected for multiple comparisons (cluster-wise correction using Gaussian random field theory with $p < .05$ and Bonferroni correction for the number of seeds).

4.3.6 Correlation analyses with behavioral measures

In *analyses I* and *II*, we correlated scores from behavioral measures with brain responses by performing regression analyses within the significant cluster from the group comparisons. In *analysis III*, we extracted the mean *z*-value from the significant clusters of the group contrasts and computed correlations with behavioral measures using the Pearson's and Spearman's correlation coefficients.

5 Summary of the related papers

5.1 Pathological gambling and alcohol dependence: neural disturbances in reward and loss avoidance processing (Analysis I)

The first analysis was conducted in order to test whether PG patients show altered brain responses by the prospect of monetary gains and losses and the notification of successful gain and loss avoidance in areas that have previously been implicated in reward processing during the MID task: the ventral striatum and medial PFC (*hypothesis 1)*. A further aim of this analysis was the direct comparison between PG and a substance-related addiction. Therefore, we analyzed data of the MID paradigm from 18 PG patients, 15 AD patients and 17 controls using BPM to consider interindividual gray matter differences.

We observed altered brain responses during monetary loss processing in PG patients as compared to healthy controls and AD patients (Figure 4A): Against our hypothesis, PG patients showed elevated brain responses in right ventral striatum during the anticipation of possible monetary loss compared to controls and AD patients. Moreover, PG patients demonstrated blunted brain responses in right ventral striatum and right medial PFC during the notification of successful avoidance of monetary loss as compared to controls, which were negatively correlated with severity of gambling behavior. In contrast to *hypothesis 1*,

we did not find any alterations during the anticipation and notification of monetary gain in PG patients.

The alterations in the encoding of loss-indicating stimuli and successful loss avoidance may be related to the PG behavior of "loss chasing". Despite the observation of altered brain responses during reward processing in brain areas, which were also implicated in substance use disorder, our results demonstrate that PG differs from a substance-related addiction in loss avoidance processing. In chapter 6, the results are further discussed with respect to the different addiction theories.

5.2 Higher volume of ventral striatum and right prefrontal cortex in pathological gambling (Analysis II)

In order to test the hypothesis that PG is associated with volumetric alterations within the PFC and mesolimbic reward system *(hypothesis 2)*, 20 PG patients and 21 matched controls were analyzed by means of VBM with the ventral striatum and right PFC as ROIs. PG subjects demonstrated a higher volume in right ventral striatum and right anterior PFC compared to controls (Figure 4B). A higher prefrontal and ventral striatal volume may reflect brain adaptations caused by excessive and repeated gambling. Moreover, the higher volume of local gray matter in right anterior PFC and right ventral striatum in the PG group were highly positively correlated, which indicates that the volumetric changes are linked to each other. In sum, the findings confirm *hypothesis 2* by demonstrating structural changes in PFC and reward system. Chapter 6 discusses the results with respect to the different addiction theories and by including the results from the other analyses.

5.3 Increased functional connectivity between prefrontal cortex and reward system in pathological gambling (Analysis III)

Since we hypothesized to find an altered resting-state functional connectivity between PFC and reward system *(hypothesis 3)*, we analyzed resting-state fMRI data from 19 PG patients and 19 controls by using seed-based functional connectivity. For the functional connectivity analysis of the middle frontal seed region, all 38 subjects were analyzed. For the functional connectivity analysis of the ventral striatal seed region, we had to exclude five PG patients and one control subject due to lack of complete brain coverage in that area; these subgroups thus consisted of 14 PG patients and 18 controls.

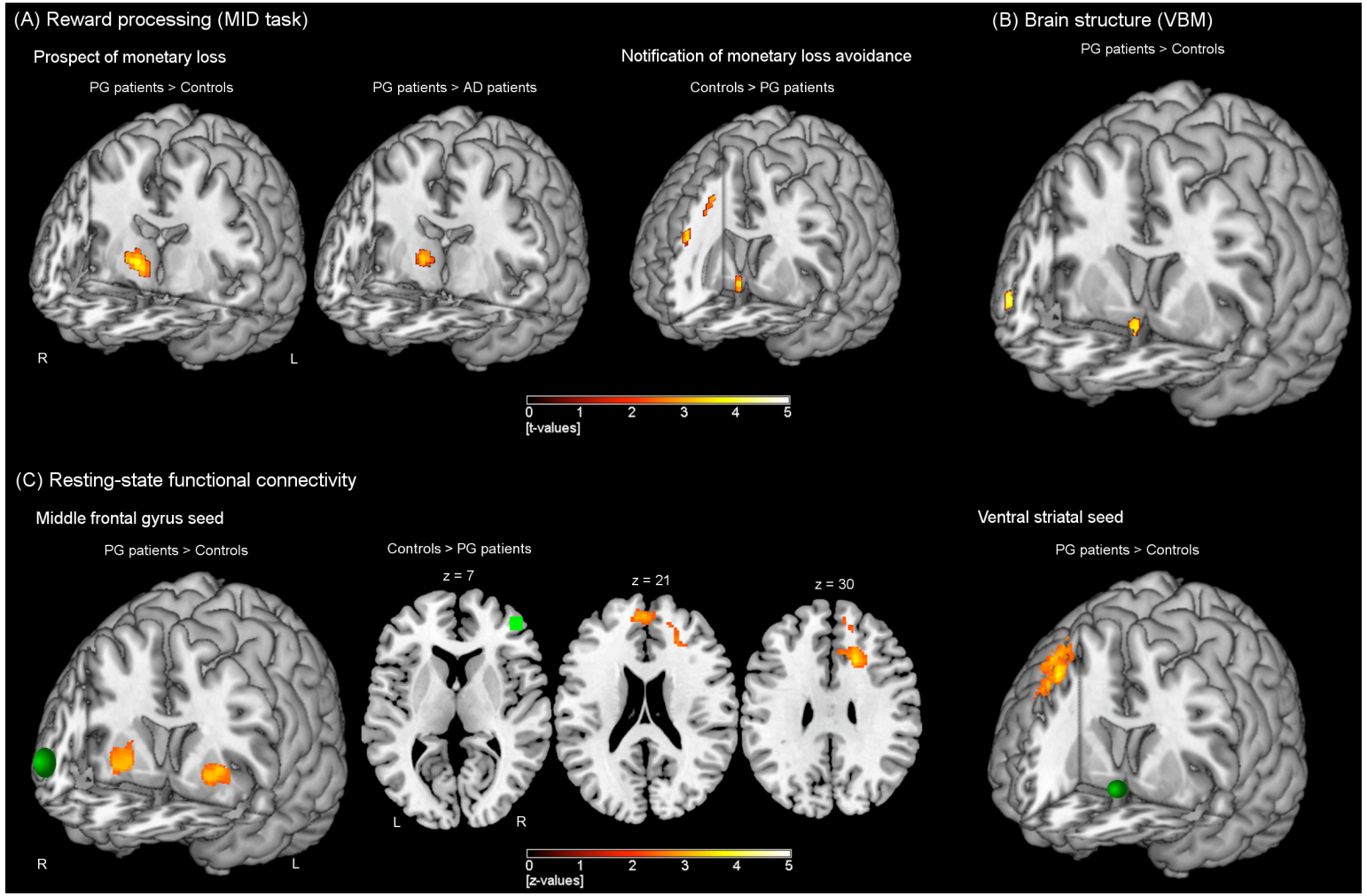

Figure 4. Results from *analyses I, II* and *III*. (A) Differences in brain response between PG patients and controls as well as PG patients and AD patients during the prospect of monetary loss within bilateral ventral striatal ROI and during the notification of monetary loss avoidance within bilateral ventral striatal and medial prefrontal ROI ($p_{FWE} < 0.05$, corrected for local gray matter volume). (B) Differences in local gray matter between PG patients and controls within bilateral ventral striatal and right prefrontal ROI ($p_{FWE} < 0.05$).
(C) Group differences in functional connectivity between PG patients and controls for right middle frontal and right ventral striatal seed (depicted in green) ($z > |2.3|$, cluster-wise corrected using Gaussian random field theory with $p < .05$, Bonferroni corrected for the number of seeds, and corrected for local gray matter volume). R, right; L, left.

There was an increased connectivity from the middle frontal seed region to the right striatum in PG patients as compared to controls. The increased connectivity was positively correlated with nonplanning aspect of impulsiveness, smoking and craving scores in the PG group. PG patients further demonstrated decreased connectivity from the right middle frontal gyrus to other prefrontal areas as compared to controls. For the right ventral striatal seed region, PG patients demonstrated increased connectivity to the right superior and middle frontal gyrus and left cerebellum as compared to controls. The increased connectivity to the cerebellum was positively correlated with smoking in the PG group. For an illustration of the main results see Figure 4C.

By demonstrating an increased functional connectivity between areas of the PFC and mesolimbic reward system, we were able to confirm *hypothesis 3* and complement the results of *analysis II*. Together, the findings suggest alterations in the information processing (both top-down and bottom-up) between PFC and ventral striatum. In addition, a decreased connectivity between prefrontal areas may reflect alterations in the organization of the PFC. Importantly, the observed connectivity alterations in cortico-striatal circuits resemble those reported for substance-related addictions (Kelly et al., 2011; Ma et al., 2010; Wilcox et al., 2011). In chapter 6, the results are further discussed by incorporating the different addiction theories and including the results of the other analyses.

6 Discussion

This thesis investigated reward processing, gray matter volume and functional connectivity in PG patients with a special focus on the PFC and ventral striatum. The main findings were (1) altered brain responses during loss avoidance processing and (2) an increased gray matter volume within PFC and striatum as well as (3) an increased functional connectivity between these two brain regions. Our findings suggest that PG is not only associated with changes in brain structure and reward processing within the PFC and reward system but also with an altered coupling between these brain regions.

The findings of this thesis contribute to the application of addiction theories to PG. Results of *analysis I* (MID) underline the importance of loss avoidance processing within the framework of learning theoretical models (e.g., Siegel, 1999). Increased neuronal encoding of loss-indicating stimuli, as present in the “prospect of loss” condition, may reflect the subject’s focus on such cues and may reinforce the gambler to continue gambling in order

to avoid money loss. Moreover, successful avoidance of losing money corresponds to negative reinforcement. A lack of adequate encoding of such successful avoidance of negative outcomes by gambling, as we observed in the "notification of successful loss avoidance" condition, may contribute to the maintenance of PG behavior (increased extinction resistance; Solomon et al., 1953). Altered processing of successful action outcomes may also help to explain, why PG patients continue to gamble in order to win back gambling losses ("chasing ones losses"; DSM-5 diagnostic criteria; American Psychiatric Association, 2013).

With respect to the reward deficiency hypothesis, increased gray matter volume in the right ventral striatum and right PFC *(analysis II)* and increased connectivity between striatum and PFC *(analysis III)* may reflect a compensation of an altered reward system. The findings from *analysis I* suggest that at least negative reinforcement (successful loss avoidance) is not effectively processed, since we found decreased ventral striatal and medial prefrontal brain responses during this condition in the PG patients. Similarly, in studies with natural rewarding stimuli (e.g., pictures with erotic or high personally relevant content) and monetary gain, PG patients showed reduced brain responses in the ventral striatum (Balodis et al., 2012; Choi et al., 2012; de Greck et al., 2010; de Ruiter et al., 2009; Reuter et al., 2005; Sescousse, Barbalat, Domenech, & Dreher, 2013).

Our findings could also contribute to the incentive-sensitization theory (Robinson & Berridge, 1993, 2001). Alterations in the processing of loss-indicating stimuli and successful loss avoidance may reflect adaptations in the brain's reward system caused by repeated confrontation to these situations. As a result, money loss avoidance becomes highly relevant to gamblers in contrast to natural rewarding situations. Increased brain volume *(analysis II)* and connectivity *(analysis III)* may also be expressions of such adaptations. However, for behavioral addictions without the effect of an exogenous drug, neuroadaptive alterations may be less pronounced, and indeed, two recent VBM studies did not find any changes in brain volume in PG patients on a whole-brain level (Joutsa et al., 2011; van Holst, de Ruiter, et al., 2012). Moreover, only one study observed enhanced ventral striatal brain responses to gambling-related pictures (van Holst, van Holstein, et al., 2012), whereas other studies did not find cue-related changes (Crockford et al., 2005; Goudriaan et al., 2010; Potenza, Steinberg, et al., 2003) or even diminished responses (Potenza, 2008) in the ventral striatum.

Regarding theories of impaired inhibitory control (Bechara, 2005; Jentsch & Taylor, 1999), increased prefrontal gray matter *(analysis II)* and decreased connectivity between prefrontal regions *(analysis III)* may reflect an alteration in the functional organization of the PFC in accordance with the results of imaging and behavioral studies on PG that report diminished ventromedial PFC activity (Potenza, Leung, et al., 2003; Tanabe et al., 2007) and impaired executive function and decision-making (Goudriaan et al., 2005, 2006a). The results of this thesis further suggest that PG may be associated with a disturbed balance between PFC and reward system as it has already been suggested for substance-related addictions (Bechara, 2005; Heatherton, 2011; Heatherton & Wagner, 2011).

Importantly, whether our findings are a predisposition or a consequence of the disorder cannot be determined by this thesis. Since neuroimaging studies have shown that extensive experience with a certain behavior may alter brain activation (Haslinger et al., 2004) and increase volume of associated brain areas (Draganski et al., 2004; Granert et al., 2011; Maguire et al., 2003), excessive gambling behavior may result in neuroadaptive processes as mentioned above. A higher prefrontal gray matter volume and an increased functional connectivity may therefore be explained as an adaptation to the higher ventral striatal gray matter volume and altered reward processing in PG, in order to enhance self-regulatory competencies over gambling impulses. However, decreased connectivity between different PFC regions and the association between increased PFC-striatal-connectivity and nonplanning aspects of impulsiveness do not support the assumption of an increased inhibitory control. Alternatively, training effects of gambling may induce easier bottom-up information processing (i.e., from ventral striatum to PFC). For example, just recently, ventral striatal prediction error signals were positively associated with fluid intelligence (Schlagenhauf et al., 2013), supporting the role of the ventral striatum in higher cognitive functions. Bearing in mind that the PFC is not only a control instance of the brain that supports social rules, higher prefrontal volume and increased connectivity between PFC and striatum may also reflect an involvement of PFC in planning and motivating of gambling behavior and a facilitated transmission of action impulses, possible represented as conscious craving in prefrontal areas. Accordingly, we found a positive correlation between increased connectivity and craving scores in the PG group. Whether these alterations are due to repeated gambling or are involved in the development of gambling behavior remains open, as we cannot make any inference regarding causal relationships.

Just recently, PG has been newly classified under the category “Substance-Related and Addictive Disorders” in the DSM-5 (American Psychiatric Association, 2013). The high

comorbidity of PG with substance use disorders (Bischof et al., 2013) underlines the relatedness of these disorders. On a neurobiological level, our findings demonstrate alterations in PG in brain structure, reward processing and functional connectivity in a brain circuitry also implicated in substance-related addiction. With respect to structural alterations, various brain regions including the PFC and striatum are affected in substance use disorders (Cardenas et al., 2007; Chang et al., 2007; Li et al., 2013; Moreno-Lopez et al., 2012; Schwartz et al., 2010; Sullivan et al., 2005; Wrase et al., 2008). In contrast to our results, most of these studies reported volume loss, which is most likely due to the direct toxic effect of the drug on the brain as in the case of ethanol (Sun & Sun, 2001). A comparison of brain structure changes is therefore difficult. However, by considering gray matter differences using the method of BPM, we directly compared reward processing in PG and AD by correcting for potential volume differences voxel-wise and found altered brain responses for both addictions within neuronal circuits associated with processing of reward. Importantly, PG patients differed from AD patients during loss avoidance processing, indicating that this aspect of reward processing may be especially relevant for PG behavior. Our investigation of intrinsic functional connectivity also revealed similarities to substance-related addictions. Increased intrinsic fronto-striatal functional connectivity has been reported for chronic heroin users (Ma et al., 2010) and abstinent cocaine users (Wilcox et al., 2011), which is also in accordance with another recent study on PG (Tschernegg et al., 2013). In sum, the overlap of neurobiological alterations within PFC and reward system and their interaction suggest that addictive disorders share several relevant neurobiological pathomechanism.

Some limitations of this thesis have to be considered: (1) Due to our hypotheses, we focused on the PFC and striatum. However, also other brain areas including the anterior cingulate (van Holst, van Holstein, et al., 2012), anterior insula (Clark, Lawrence, Astley-Jones, & Gray, 2009) or the cerebellum (Power, Goodyear, & Crockford, 2012) may also be highly relevant for maladaptive gambling behavior. Moreover, the thalamus can also play a role, since fronto-striatal circuits are interconnected via this brain region (Alexander, DeLong, & Strick, 1986). (2) We only included male participants in order to allow for a high homogeneity within the studied sample since gender differences in symptom pattern, sociodemographic and clinical parameters are present in PG (Blanco, Hasin, Petry, Stinson, & Grant, 2006), suggesting gender differences also in neurobiological correlates. (3) Generalizability is also limited because PG patients were neither abstinent nor in therapy. Comparison to other studies on substance dependence is

therefore difficult, as they have been largely conducted with patients in an abstinent state (e.g., Beck et al., 2009; Kelly et al., 2011; Wilcox et al., 2011).

In conclusion, this thesis demonstrates that a behavioral addiction such as PG is associated with changes in loss processing and brain structure within the PFC and reward system and an altered coupling between these brain regions. The findings have implications for the treatment of PG. As already suggested by Volkow et al. (2003) for drug addiction, an imbalance between prefrontal function and the mesolimbic reward system in PG may be treated by interventions that decrease the rewarding value of gambling and increase the value of conventional reward, such as euthymic therapy (Lutz, 2005), and interventions that strengthen frontal control, such as specialized cognitive behavioral therapy (Goldapple et al., 2004). With respect to future research, longitudinal studies with risk populations are needed to answer the question whether functional alterations and brain structure changes can be considered as a risk factor for PG or if they develop throughout the illness. Moreover, potentially influencing factors, such as gender, abstinence or gambling preferences, should be taken into account in future studies.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe;

dass ich die Doktorarbeit an keiner anderen Universität eingereicht habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze; und

dass mir die zugrunde liegende Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät II vom 17.01.2005, zuletzt geändert am 13.02.2006, veröffentlicht im Amtlichen Mitteilungsblatt der HU Nr. 34/2006, bekannt ist.

Berlin, Dezember 2014

Saskia Quester